4,4'-Methylenebis-(2-Chlorobenzenamine)
(MOCA, MBOCA)
(CAS No. 101-14-4)
TEST PLAN

Submitted to the US Environmental Protection Agency

By

MBOCA Consortium

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SUMMARY

The MBOCA Consortium has sponsored 4,4'-Methylenebis-(2- chlorobenzenamine) (MOCA, MBOCA; CAS No. 101-14-4) under the EPA's High Production Volume (HPV) Program. This document provides the Test Plan and summaries of existing data for this substance.

1.0 INTRODUCTION

The MBOCA Consortium has voluntarily committed to participate in the Environmental Protection Agency's (EPA) high production volume chemicals (HPV) challenge program, to assess the health and environmental effects, including selected physical chemical characteristics of 4,4'-Methylenebis-(2- chlorobenzenamine) (MOCA, MBOCA; CAS No. 101-14-4).

An evaluation of the available data and proposed test plan are included in this document. Robust summaries are attached in Appendix 1.

The objective of this test plan is to evaluate the available data and determine what additional data, if any, are needed to adequately characterize the physical properties, environmental fate, and human health and environmental hazards of MOCA. It is proposed that additional studies be conducted as shown in Table 1.

Table 1: PROPOSED TESTING FOR MOCA; CAS NO. 101-14-4

Endpoint	Data
Physical Chemical Properties	
Melting Point	A
Vapor Pressure	A
Boiling Point	A
Partition Coefficient	A
Water Solubility	A
Environmental Fate	
Hydrolysis	A
Photodegradation	A
Biodegradation	A
Environmental Transport	A
Ecotoxicity	
Acute Fish	A
Acute Daphnia	A
Acute Algae	A
Mammalian toxicity	
Acute Oral	A
Acute Dermal	A
Repeated Dose	A
Genotoxicity (*in vitro* -bacteria)	A
Genotoxicity (*in vivo*)	A
Reproductive/Developmental	Test (OECD 422)

A= Adequate data
Test = Testing proposed

2.0 POTENTIAL USE AND EXPOSURE

MOCA is used in the United States as a curing agent in manufacturing castable polyurethane products. During 1995, about two million pounds of the chemical were used in castable polyurethane processing. This MOCA was supplied by Japanese and

Taiwanese producers since no MOCA has been manufactured in the United States since 1979.

MOCA is an important chemical as adequate substitute curatives have not been found for certain MOCA cured polyurethane products. MOCA cured polyurethane produces a tough abrasion-resistant polymer not duplicated in polyurethane manufactured with other curatives. MOCA also provides unusual processing characteristics important to producing certain products.

The Polyurethane Manufacturers Association ("PMA") represents the castable polyurethane industry and has been involved with governmental agencies and non-governmental bodies regarding regulatory matters involving MOCA since 1973. MOCA has been classified as a "carcinogen" since the early 1970s. This classification is based upon test results with laboratory animals. The American Conference of Governmental Industrial Hygienists ("ACGIH") as recently as 1992 after reviewing existing information continued the classification of MOCA as a "Suspect Human Carcinogen."

Since the 1970s industry has developed an effective program to control employee exposure to the chemical and to monitor that exposure. Governmental agencies including the Occupation Safety & Health Administration ("OSHA") and the Environmental Protection Agency ("EPA") have been complimentary of this industry program (www.mocahome.org)

3.0 EVALUATION OF EXISTING DATA AND PROPOSED TESTING

The available data have been assessed (see Tables 2 through 5). Robust summaries are provided as Appendix 1.

Chemical/Physical Properties:

The melting point of MOCA is 102-107 °C (Aldrich, 2000-2001). This is in good agreement with the EPIWIN modeled value of 110 °C (The Merck Index, 1983). The boiling point is estimated to be 378.9 °C (SRC ,1988). The vapor pressure is 0.0000133 hPa (Smith and Woodward, 1983). The calculated partition coefficient is 3.61-3.9 (Leo, 1978). The water solubility of MOCA is 13.9 mg/L at 24 °C (Voorman and Penner, 1986). The EPIWIN modeling summary is provided in Appendix 2.

TABLE 2: PHYSICAL CHEMICAL PROPERTIES FOR MOCA; CAS NO. 101-14-4

Endpoint	Result
Melting Point	102-107 °C
Vapor Pressure	.0000133 hPa at 25 °C
Boiling Point	378.9 °C
Partition Coefficient	3.61-3.9
Water Solubility	13.9 mg/L at 24 °C

Recommendation: No additional testing is proposed.

Environmental Fate:

EPIWIN was used to predict the photodegradation and environmental distribution (see Appendix 2 for EPIWIN summary). The Overall OH Rate Constant is 77.5166 E-12 cm3/molecule-sec and the predicted half-life is 0.138 days (US EPA, 2003). Level III fugacity modeling indicates distribution to soil will predominate (US EPA, 2003). The hydrolysis of the sponsored substance is slow (USEPA, 1988). MOCA does not biodegrade (Chemicals Inspection and Testing Institute, 1992).

Recommendation: No further testing is proposed.

TABLE 3: ENVIRONMENTAL FATE DATA FOR MOCA; CAS NO. 101-14-4

Endpoint	Result
Hydrolysis	Half-life > 1 year
Photodegradation	Overall OH Rate Constant = 77.5166 E-12 cm3/molecule-sec Half-Life = 0.138 days
Biodegradation	0% after 28 days
Environmental Transport (Level III Fugacity modeling)	Air 9.87e-005 Water 15.5 Soil 82.1 Sediment 2.42

Aquatic Toxicity:

Acute aquatic toxicity data are available for fish, daphnia and algae for the sponsored substance. Although details of these studies are not readily available, the studies were conducted by Japanese MOE and these studies are widely accepted as valid. The 96 hour LC50 to fish (*Oryzias latipes*) was 0.61 mg/L (National Institute of Technology and Evaluation, Ministry of the Environment, 2001). The 48 hour LC50 for *Daphnia magna* is 0.92 mg/L (National Institute of Technology and Evaluation, Ministry of the Environment, 2001). In algae (*Selenastrum capricornutum*) the 48 hr ECr50 and 72 hr ECb50 are both > 1.9 mg/L. The 48 and 74 hour NOEC's are 1.4 and 0.74 mg/L, respectively (National Institute of Technology and Evaluation, Ministry of the Environment, 2001).

A 21 day reproduction study with *Daphnia magna* has been conducted by the Japanese MOE. The 21 day EC50 and NOEC are 0.052 and 0.0095 mg/L, respectively (National Institute of Technology and Evaluation, Ministry of the Environment, 2001).

TABLE 4: ENVIRONMENTAL EFFECTS DATA FOR MOCA; CAS NO. 101-14-4

Endpoint	Result
96 hr LC50 Fish (mg/L)	0.61
48 hr LC50 Daphnia (mg/L)	0.92
96 hr EC50 Algae (mg/L)	ECr50 >1.9 ECb50 >1.9
Chronic Daphnia (21 d EC50) (mg/L)	0.052

Recommendation: No additional testing is proposed.

Acute Mammalian Toxicity:

Acute oral and dermal studies have been conducted. The acute oral LD50 in rats is 1140 mg/kg (Lewis, 1996). The dermal LD50 in rabbits is greater than 5000 mg/kg (Lewis, 1996).

Recommendation: No additional testing is proposed.

Repeated Dose/ Reproductive/Developmental Toxicity:

Standard repeated dose toxicity studies have not been conducted with MOCA. However, extensive cancer studies have been conducted from which the toxicity of this substance can be described.

Rats were fed 12.5, 25 or 50 mg MOCA/kg/day on standard protein diet or 6.25, 12 or 25 mg MOCA/kg/day on low protein diet for 18 months (Kommineni et al., 1979). A dose-dependent increase in lung tumors was observed in rats fed 12.5, 25, or 50 mg/kg/day of MBOCA for 18 months; the incidence of lung tumors was 23%, 37%, and 70%, respectively (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry). In contrast, the incidence of lung tumors in rats was lower if animals were fed MBOCA in a protein-deficient diet. In rats fed 6.25, 12, or 25 mg/kg/day of MBOCA in a low protein diet for 18 months, the incidences of lung tumors were 6%, 15%, and 26%, respectively, while no tumors were found in control animals. These numbers are less than half of the incidences reported for comparable doses of MBOCA given to rats fed a standard diet. MBOCA also induces liver tumors in rats. An increase in the incidence of hepatomas was found in rats fed 25 or 50 mg/kg/day of MBOCA in a standard protein diet for 18 months; the incidences were 4% and 36%, respectively. The effect of standard and low protein diets on the incidence of MBOCA-induced hepatocellular carcinomas was investigated in rats. In Sprague-Dawley rats fed 12.5 or 25 mg/kg/day of MBOCA in a standard protein diet for 18 months, the incidences of hepatocellular carcinomas were 3% and 4%, respectively; in rats fed the same amounts of MBOCA in a protein-deficient diet, the incidences were 0% and 18%, respectively. These results indicate that a protein-deficient diet did not reduce the MBOCA-induced incidence of hepatocellular carcinoma

in rats. A similar finding was made in male rats fed 25 mg/kg/day of MBOCA in a low protein diet for 18 months; the incidence of mammary tumors was 6%. When rats were fed a standard diet, the incidence of mammary adenocarcinoma was 28% at 50 mg/kg/day of MBOCA and 11% at 25 mg/kg/day. Zymbal's gland carcinomas were found in 12% of rats fed a low protein diet and in 7% of rats fed a standard-protein diet; both diets contained 25 mg/kg/day MBOCA. The results in rats fed MBOCA in low and standard protein diets indicate that there is a dose-related increase in the incidence of lung and mammary carcinomas, while the incidence of hepatocellular carcinoma is not dose-related. Other tumor types were also found after chronic oral administration of MBOCA. The incidence of hemangiosarcomas was 4% and 8% in rats fed 25 mg/kg/day of MBOCA in standard protein or low protein diets, respectively. The incidence of pituitary adenomas (including adenocarcinomas) in rats fed a standard protein diet was reduced, especially in animals treated with high doses of MBOCA. Rats fed 12.5, 25, or 50 mg/kg/day of MBOCA for 18 months had 36%, 25% (statistically significant), and 4% (statistically significant) incidences of pituitary adenomas, respectively. The incidence of pituitary adenomas in the control group was 42%. MBOCA had an effect on the incidence of pituitary tumors in rats fed a low protein diet: the incidences were 16%, 12% (statistically significant), and 20% in animals fed 6.25, 12.5, and 25 mg/kg/day, respectively. In the control group, the incidence of pituitary adenomas was 23%.

Rats were fed 50 mg MBOCA/kg/day in standard protein diet or 50 mg MBOCA/kg/day in low protein diet for two years (Stula et al., 1975). The effect of standard and low protein diets on the incidence of MBOCA-induced lung adenocarcinomas was investigated in rats: the incidence of lung tumors in rats fed a protein-deficient diet was roughly one-half of that observed in rats fed a standard protein diet (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry). The effect of standard and low-protein diets on the incidence of MBOCA-induced hepatocellular carcinomas was investigated in rats. The results are inconclusive. When male rats were fed 50 mg/kg/day of MBOCA for 2 years, the incidences of hepatocellular carcinomas were 7% in rats fed a standard-protein diet and 52% in rats fed a low protein diet. This observation, that the protein-deficient diet accentuates the carcinogenic effects of MBOCA, was not seen in female rats that had 7% and 5% hepatocellular carcinomas when fed standard-protein and low-protein diets, respectively. A statistically significant increase of malignant mammary tumors was found in female Charles River rats fed 50 mg/kg/day of MBOCA in a low-protein diet for 2 years. A statistically significant decrease in pituitary tumors was also observed in female, but not male, rats.

Male rats were fed 25 or 50 mg MBOCA/kg/day in a standard protein diet for18 months (Russfield et al., 1975). Lung adenocarcinomas were reported in 1/22 and 1/19 animals, respectively, although this finding was not statistically significant (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry). In addition, 3 of 22 and 4 of 19 rats receiving 25 or 50 mg/kg/day of MBOCA, respectively, developed adenomatosis, which is a

preneoplastic lesion. MBOCA also induced liver tumors in rats. An increase in the incidence of hepatomas was found; the incidences were 5% and 21%, respectively (not statistically significant). A limitation of this study is the small number of animals on which the tumor incidence was based.

Mice were fed 130 or 260 mg/kg/day for 18 months, and followed for an additional 6 months post-exposure (Russfield et al., 1975). MBOCA induced liver tumors in mice. There was a significantly increased incidence of hepatomas, 43% in the 130-mg/kg/day group and 50% in the 260-mg/kg/day group was reported (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry). The incidence of hepatomas in treated random-bred male albino mice was not significantly different from that in controls. These results indicate that in mice there is a gender difference regarding MBOCA-induced hepatomas; female mice are affected, and male mice are not affected. Vascular tumors (generally subcutaneous hemangiomas and hemangiosarcomas) were reported in randomly bred male albino mice fed 130 or 260 mg/kg/day of MBOCA for 18 months; the incidences were 23% and 40%, respectively. In female mice, vascular tumors (43%) were present only in the group treated with the high dose of 260 mg/kg/day of MBOCA.

Rats were fed 54 mg MBOCA/kg/day in a low protein diet for 500 days (Grundmann and Steinhoff, 1970). 32% of males and 12% of females developed lung tumors. Liver cancer was present in 88% of males and 72% of females (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry).

Beagle dogs were fed 10 mg MBOCA /kg/day for 9 years (Stula et al., 1977). One beagle died approximately 3.4 years of pyelonephritis unassociated with MBOCA exposure. Of the five surviving dogs, three developed papillary transitional cell carcinomas of the urinary bladder; and one dog had a combined urethral adenocarcinoma and transitional cell carcinoma (results excerpted from ATSDR (1994) Toxicological Profile for 4,4'-Methylene-bis(2-chloroaniline) MBOCA; U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry). Despite the small number of animals used, this study demonstrates that ingestion of MBOCA over 9 years was associated with the appearance of carcinomas of the urinary bladder and urethra in dogs.

Male rats were fed diets containing 0, 500 or 1000 mg/kg of diet MOCA as the hydrochloride (97% pure) for 18 months (IARC, 1993). All surviving animals were killed 24 months after the start of the study; about 55% of the control and treated animals were still alive at 20-22 months. The effective numbers were: 22 control, 22 low-dose and 19 high-dose animals. Hepatomas occurred in 0/22 control, 1/22 low-dose and 4/19 high-dose rats.

Groups of rats were fed 0 (control) or 1000 mg/kg of diet MOCA (approximately 95% pure) in a standard diet (23% protein) for life (IARC, 1993). The average duration of the experiment was 560 days (80 weeks) for treated males, 548 days (78 weeks) for treated females, 564 days (80 weeks) for male controls and 628 days (89 weeks) for female controls. Six animals from each group were sacrificed at one year for interim evaluation. Lung adenocarcinomas occurred in 21/44 ($p < 0.05$, 2 test) treated males and 27/44 ($p < 0.05$, 2 test) treated females. An additional squamous-cell carcinoma of the lung was observed in one treated male and one treated female. No lung tumor was observed among control animals. Lung adenomatosis, considered to be a preneoplastic lesion, developed in 14/44 treated males and 11/44 treated females and in 1/44 male controls and 1/44 female controls ($p < 0.05$). Pleural mesotheliomas occurred in 4/44 treated males and 2/44 treated females; no such tumor was observed among controls. Hepatocellular adenomas and hepatocellular carcinomas occurred in 3/44 and 3/44 treated males and in 2/44 and 3/44 treated females, respectively, but not in controls. Ingestion of MOCA resulted in a lower incidence of pituitary tumors in treated females than in controls (1/44 versus 12/44).

No reproductive toxicity or developmental studies have been conducted with MOCA.

Recommendation: A combined repeat dose with developmental and reproductive screen (OECD 422) is proposed to fulfill a standard repeat dose toxicity endpoint as well as reproductive toxicity and developmental effects.

Mutagenicity Assays:

In vitro testing indicates that MOCA is mutagenic in the *Salmonella typhimurium* /mammalian microsome mutagenesis assay and that the mutagenic effect requires exogenous metabolic activation (Ames et al., 1975; ATSDR, 1994; Baker and Bonin, 1981; Butler et al., 1989; Chen et al., 1989; Cocker et al., 1985; 1986; Dunkel et al., 1984; Hesbert et al., 1985; Kuslikis et al., 1991; MacDonald, 1981; Martire et al., 1981; Matsushima et al., 1981; McCann et al., 1975; Messerly et al., 1987; Morton et al., 1988; Rao et al., 1982; and Walker, 1984). In vivo animal studies provide direct and indirect evidence that MOCA is a mutagen (ATSDR, 1994; Caspary et al., 1988; Cheever et al., 1990; Daniel and Dehnel, 1981; Dunkel et al., 1984; Galloway et al., 1985; Katz et al., 1981; Kugler-Stegmeier et al., 1989; Martin and McDermid, 1981; McQueen et al., 1981; 1983; 1987; Mori et al., 1988; Myhr and Caspary, 1988; Perry and Thomson, 1981; Salamone et al., 1981; Styles, 1981; Traul et al., 1981; Tsuchimoto and Matter, 1981; Vogel et al., 1981; and Williams et al., 1982).

Recommendation: No additional testing is proposed.

TABLE 5: MAMMALIAN TOXICITY DATA FOR MOCA; CAS NO. 101-14-4

Endpoint	Result
Acute Oral LD50 (mg/kg)	1140 (rat)
Acute Dermal LD50 (mg/kg)	>5000 (rabbit)
Repeated Dose	NOAEL (18 mo dietary, standard protein diet, cancer, rat) = 6.25 % LOAEL (18 mo dietary, low protein diet, cancer, rat) = 12.5 % LOAEL (2 yr dietary, standard or low protein diet, systemic toxicity, rat) = 50 mg/kg/d LOAEL (2 yr dietary, standard or low protein diet, cancer, rat) = 50 mg/kg/d LOAEL (18 mo dietary, standard protein diet, systemic toxicity, rat) = 25 mg/kg/d LOAEL (18 mo dietary, cancer, rat) = 25 mg/kg/d LOAEL (18 mo dietary, cancer, mouse) = 130 mg/kg/d LOAEL (500 d dietary, low protein diet cancer, rat) = 54 mg/kg/d LOAEL (9 yr dietary, systemic toxicity, dog) = 10 mg/kg/d LOAEL (9 yr dietary, cancer, dog) = 10 mg/kg/d LOAEL (18 mo dietary, cancer, rat) = 500 mg/kg/d LOAEL (lifetime dietary, standard protein diet, cancer, rat) = 1000 mg/kg/d
Genotoxicity (*in vitro* - bacteria)	Positive
Genotoxicity (*in vivo*)	Positive
Reproductive/Developmental	No data available

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